

REMARKS/ARGUMENTS

Status of the claims

Claims 1, 3, 5, 11, and 13 are pending. Claims 2, 9, 10, and 12 are canceled. New claim 13 is added and claims 1 and 3 are amended. Support for immunostimulating variants and fragments of SEQ ID NO:2 can be found, *e.g.*, on page 11, line 5 through page 13, line 10 of the specification as filed. Support for one or more adjuvants can be found, *e.g.*, on page 20, line 27 to page 21, line 18, and page 41, line 32 to page 42, line 15. No new matter is added.

Rejection under 35 USC § 112, first paragraph – Written description

The Examiner has rejected claims 1-3, 5, and 9-12 as allegedly failing to comply with the written description requirement. According to the Examiner, the application fails to identify variants of SEQ ID NO:2 that provide immunity against FIPV in a subject.

The fundamental factual inquiry for written description is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, that the applicant was in possession of the claimed invention (*see* MPEP 2163.02).

Claim 1 is amended to specify that the vaccine comprises a polypeptide comprising SEQ ID NO:2 or a defined variant thereof which can immunologically stimulate immunocompetent cells. New claim 13 describes a vaccine comprising a polypeptide comprising SEQ ID NO:2, or a immunostimulating fragment of SEQ ID NO:2 having 45 or more continuous amino acids.

The present examples demonstrate successful use of the polypeptide of SEQ ID NO:2 as a vaccine (*see* section starting on page 41, line 32). The disclosure on pages 11-15 demonstrates that the inventors envisioned use of variant and partial sequences of SEQ ID NO:2 as vaccine compositions. The section explains that highly homologous proteins have similar immunological characteristics, and that the protein used in the vaccine need not include the entire structure of the full length antigen protein as long as it can immunologically stimulate

immunocompetent cells. Epitopes, and epitope determination methods, are described on page 13.

It is routine in the art to introduce slight variations to a protein sequence that has been found to be immunogenic in order to optimize the effect on cellular immunity, or minimize undesired effects. The specification explains to one of skill that variations can be introduced to the immunostimulating protein of SEQ ID NO:2, and easily compared for effect. For example, page 15 explains that immune activation can be tested using routine CTL assays.

These disclosures demonstrate that the inventors were fully in possession of the claimed vaccines to provide immunity against FIVP. In view of the foregoing comments, Applicants respectfully request withdrawal of the rejection under the first paragraph of 35 USC § 112 for written description.

Rejection under 35 USC § 102

The Examiner has rejected claims 2 and 9 as allegedly anticipated by Motokawa *et al.* (1996) *Microbiology and Immunology* 40:425-33. In an effort to expedite prosecution, claims 2 and 9 are canceled, thereby obviating the rejection. As explained in more detail below, cancelation of the claims does not indicate Applicants' acceptance of the reasons for rejection.

Applicants respectfully request withdrawal of the rejection under 35 USC § 102.

Rejections under 35 USC § 103

Wasmoen in view of Motokawa

The Examiner has maintained the rejection of 2, 9-10, and 12 as allegedly obvious over Wasmoen *et al.* (US5770211) in view of Motokawa. The Examiner alleges the evidence submitted by Applicants with the April 13, 2009 response (German *et al.*) was not persuasive. According to the Examiner, German discusses feline corona virus vaccines in general, and only describes a vaccinia virus expressing the S protein. Applicants respectfully disagree for the reasons set forth below.

Legal standard

MPEP 2142 states that rejections for obviousness cannot be sustained with mere conclusory statements. The burden is on the examiner, in view of all factual information, to provide some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. The examiner must provide evidence which **as a whole** shows that the legal determination sought to be proved is more probable than not.

The legal concept of *prima facie* obviousness allocates who has the burden of going forward with production of evidence in each step of the examination process. **The examiner bears the initial burden** of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. If, however, the examiner does produce a *prima facie* case, the burden of coming forward with evidence or arguments shifts to the applicant, who may submit additional evidence of nonobviousness (MPEP 2142). Such evidence can include secondary considerations such as **long felt, but unsolved need, failure of others, and unexpectedly successful results**. MPEP 2141.02 again emphasizes that **prior art must be considered in its entirety**, including disclosures that teach away from the claims.

Arguments

Applicants respectfully disagree with the Examiner's assessment of the prior art **as a whole at the time of the invention**. The first paragraph of German explicitly discloses that attempts at making vaccines using the **type I N protein** have not been successful.

Feline infectious peritonitis (FIP) is a fatal disease of cats caused by feline coronavirus (FCoV) infection. There are two serotypes, type I being more prevalent in field conditions (Hohdatsu et al., 1992), accounting for at least 70% of FIP cases. However, to date, most vaccine attempts have been largely unsuccessful, with traditional approaches sometimes serving to exacerbate disease through antibody dependent enhancement (ADE). The identification of FCoV epitopes responsible for neutralization and enhancement is still under investigation. Attempts at vaccination have included the use of avirulent FCoV, recombinant vaccinia virus expressing the S protein, non-feline coronaviruses and **plasmids expressing M or N proteins alone**, or

with enhancement through vaccinia viruses or feline cytokines.
(emphasis added, citations omitted)

German, published six years after Wasmoen, demonstrates the failure of others to design a type I N protein vaccine against FIPV. Applicants submitted additional evidence to this effect with the April 13, 2009 response. The editorial from Horzinek, a respected feline coronavirus expert, indicates that, as of 2004, vaccine design efforts had been largely unsuccessful. Hodatsu *et al.*, in a report on the present invention, indicated the surprising nature of the present results using a vaccine based on the type I N protein. To repeat the quote from page 50:

In a study published last December, cats had been immunized with recombinant baculovirus-expressed N protein of a Type I FIPV; they produced homologous antibodies, but of course, no virus-neutralizing ones. A DTH skin response to N [protein] was observed in the vaccinated cats, so cellular immunity had kicked in, and when they were challenged with heterologous FIPV, survival amounted to 75%, which is very high for this type of experiment. *(emphasis added)*

The Examiner has repeated the contention that it would be obvious to design a vaccine against type I N protein, in part because it was known that type I was more common than type II.

Applicants have demonstrated that, while there was a long felt, but unmet, need for such a vaccine, previous attempts at creating this vaccine had been unsuccessful. A report from the inventors' peers demonstrates the surprising nature of the results presented herein.

Claims 2, 9-10, and 12 are canceled herein, thereby rendering the rejection based on Wasmoen and Motokawa moot. However, the arguments apply equally to the new obviousness rejection, which we turn to now.

Wasmoen in view of Motokawa and Duphar (EP0411684A2)

The Examiner has newly rejected claims 1-3, 5, and 9-12 based on Wasmoen, in view of Motokawa and Duphar. According to the Examiner, Duphar teaches a vaccine against

FIPV comprising the amino acid sequence of the N protein. The Examiner alleges that it would therefore be obvious to formulate a FIPV vaccine using an N protein of SEQ ID NO:2.

Applicants respectfully traverse the rejection for the reasons explained above. Wasmoen teaches use of the N protein from a type II FIPV in a vaccine. Motokawa teaches the sequence of SEQ ID NO:2 from the present application, *i.e.*, the N protein from a type I FIPV. Motokawa does not suggest use of the protein for a FIPV vaccine. Duphar is cumulative of Wasmoen. That is, Duphar merely teaches a vaccine comprising a type II FIPV N protein, a protein with different antigenicity than the protein from a type I FIPV.

Nothing in these references would provide one of skill at the time of the invention with a reasonable expectation of success in vaccinating cats against FIPV with a type I N protein. As explained above and in the responses dated July 31, 2008 and April 13, 2009, the art at the time of filing disclosed that, while type I FIPV was more common, repeated attempts to design a vaccine against type I FIPV had been unsuccessful. In addition, as explained on page 6 of the specification, type I FIPV is difficult to work with, as it is less pathogenic and grows more slowly than type II.

Yet, despite various technical hurdles, the inventors have demonstrated successful use of the N protein of type I FIPV in a vaccine administered to cats. The examples demonstrate that the vaccine conferred cellular immunity to both type I and type II FIPV. As explained above, the inventors' scientific peers acknowledged that the rate of successful vaccination from the present invention was unexpectedly high.

Claim 1, as amended, describes a vaccine comprising the protein of SEQ ID NO:2 or a defined immunostimulating variant thereof, in combination with one or more adjuvants. One of skill, considering the knowledge available at the time as a whole, would not be motivated to combine the type I N protein with an adjuvant to confer cellular immunity to FIPV. Indeed, the art indicated that such attempts would be unsuccessful.

In view of the unexpected results disclosed in the present specification, and the failure of others to design a successful vaccine against type I FIPV, Applicants respectfully request reconsideration of the rejections under 35 USC § 103.

Appl. No. 10/520,333
Amdt. dated November 11, 2009
Reply to Office Action of June 17, 2009

PATENT

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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